DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
COMMENTS BEFORE THE NONPRESCRIPTION
DRUG ADVISORY COMMITTEE

September 3, 2002

Background Package submitted by the ASPIRIN FOUNDATION OF AMERICA, INC.

Meeting Topic: NDAC Meeting on September 20, 2002 re: safety of Aspirin products

INTRODUCTION

The Aspirin Foundation of America, Inc. ("Aspirin Foundation" or "Foundation"), is a not-for-profit industry organization comprised of the principal producers of aspirin and aspirin-containing products in the United States. It was formed to facilitate and encourage an understanding of the health benefits of aspirin use, based upon sound data and good science. The Aspirin Foundation supports the Food and Drug Administration's ("FDA") efforts to finalize the monograph for Internal Analgesic, Antipyretic and Antirheumatic OTC products (the "IAAA monograph"), and its continuing efforts to ensure the safety and efficacy of medications for consumers. The Aspirin Foundation also supports FDA's ongoing efforts to modernize and simplify OTC product labeling and make it more informative and consumer friendly.

For the past 21 years the Aspirin Foundation has been actively working with FDA to help ensure that the regulation of aspirin labeling is based on sound scientific principles and good data. It has provided data to help the agency establish the IAAA monograph and concomitant labeling for aspirin products. The Foundation has served as the aspirin industry's spokesman with FDA and other government agencies, and has assisted FDA from time to time over the past two decades at the agency's request on matters relating to aspirin.

For example, in the 1980's the Foundation worked closely with FDA to develop a regulatory response to Reye's Syndrome. At FDA's request, the Foundation developed a consensus in the industry for voluntary label warnings, while scientific research was being conducted. It helped fund and oversaw the research, conducted a nation-wide public education program and ultimately helped create a regulatory label warning program. In the 1990's the Aspirin Foundation petitioned FDA to add the use of aspirin for the treatment of acute myocardial infarction, providing key data from European studies which FDA needed for its assessment. At FDA's request the Foundation sought data from studies on low-dose aspirin to assist in the development of the final rule on professional indications for aspirin. The Aspirin Foundation also took part in the previous meeting of the Nonprescription Drugs Advisory Committee in 1993 relating to the use of analgesics among heavy drinkers.

I. ANY NEW LABEL WARNINGS ON ASPIRIN PRODUCTS MUST BE BASED ON SAFETY CONCERNS FOR ASPIRIN.

It is clear that whatever decisions FDA reaches on the need for additional label warnings for the safe and effective use of aspirin, they must be based on the agency's concerns about the safe and effective use of aspirin. Concerns about possible consumer shifts from or to aspirin products due to possible concerns about label warnings on competing analgesics can have no impact on the agency's decisions regarding what warnings to require on aspirin labels.

The rules under which FDA must determine whether additional warnings are needed are clear. As the agency itself has said: "warning statements for OTC drugs should be limited to those that are scientifically documented, clinically significant and important for the safe and effective use of the products by consumers." 53 Fed. Reg. 46204, 46213 (Nov. 18, 1988)(Tentative Final Monograph for IAAA OTC products). Thus, a decision that additional warnings are needed on aspirin, over and above the current label warnings, must

be based on "scientifically documented, clinically significant" data such that new warnings are "important for the safe and effective use of [aspirin] by consumers."

The Aspirin Foundation believes it would be inappropriate to require warnings on aspirin simply to have uniform "class" warnings on OTC analgesics. Any decision in support of such warnings would be contrary to the principles announced by FDA in proposing the Tentative Final Monograph (as quoted above). Indeed, class warnings would have the potential of diminishing the impact of the warnings that are truly necessary, as consumers would be less likely to heed a warning that is found on all products, regardless of the level of risk.

II. ASPIRIN HAS A LONG HISTORY OF SAFETY FOR CONSUMER USE

The Aspirin Foundation encourages FDA to apply these principles to the available data relevant to the safe and effective use of aspirin. While the Foundation encourages the agency to take steps necessary to protect the safety of consumers, it also notes that aspirin itself has had an exhaustive list of warnings on its label for many years. We are unaware of new data since 1987 that are scientifically documented, clinically significant and important for the safe and effective use of aspirin by consumers and which support an addition to the already-extensive list of warnings on aspirin. Aspirin is a proven analgesic that has been used safely by millions of consumers for over 100 years. Sound science supports the safety and efficacy of aspirin when used as currently labeled.

It is important to keep in mind the results of previous expert advisory reviews of aspirin. In FDA's 1977 Advanced Notice of Proposed Rulemaking ("1977 ANPR"), which reported the conclusions of the FDA Advisory Review Panel (the "Panel"), the Panel found that:

> [I]n light of [ ] extensive use and long marketing history [of aspirin] and the relatively low incidences of serious toxic

> effects associated with short term use of presently recommended doses; the safety of aspirin has been well-established for the majority of the population and the risk benefit ratio is low.

42 Fed. Reg. 35246, 35383 (July 8, 1977). The same holds true today – aspirin, as currently labeled, is used on a regular basis by consumers with low incidence of adverse effects.

A. Labeling For OTC Aspirin Products Is Currently Sufficient to Allow the Safe Use by Consumers

OTC labeling of aspirin products currently includes warnings relating to the potential for GI bleeding, alcohol and allergy warnings, and general warnings relating to symptoms of aspirin overdose and side effects. At this time, we are aware of no evidence of adverse effects that is "scientifically documented, clinically significant and important" and for which additional warnings are needed. There is no evidence which indicates that the current warnings are insufficient to allow proper and safe use of aspirin products by consumers or that additional label information would better inform the public of risks associated with taking aspirin. Therefore, the evidence supports the option that no additional action be taken to change current labeling.

1. Current OTC Labeling Regarding the Potential for Gastrointestinal Effects is Sufficient to Inform Consumers of Potential Risks from Aspirin Use.

OTC products containing aspirin currently bear the warning:

> Do not take this product if you have stomach problems (such as heartburn, upset stomach or stomach pain), or if you have ulcers or bleeding problems that persist or recur, unless directed by a doctor.

This is a specific warning telling consumers what to do – not to take aspirin – if they have any of these gastrointestinal conditions or symptoms, or bleeding.

For years this warning has been used to alert consumers of the effects of aspirin on the stomach. In addition, advertising by competitors has reinforced consumer

understanding of adverse gastrointestinal effects. An alcohol warning was added in 1999. There is currently no evidence that these warnings have been insufficient to warn consumers of the potential risks when taking products that contain aspirin.

2. Other Label Information and Warnings on Aspirin Are Sufficient to Allow Safe Use of the Product.

Aspirin products currently include pregnancy warnings, warnings against use of the products when certain other medications are being taken except under a doctor's care and warnings against use by children and teenagers with chicken pox and flu symptoms before a doctor is consulted about Reye's Syndrome. As noted above, aspirin products also contain organ-specific warnings relating to the potential for gastrointestinal bleeding in consumers with stomach problems and other conditions. Thus, the current labeling contains warnings that provide consumers with adequate information to evaluate the risks of taking aspirin: the current labeling: a) lists symptoms which may be exacerbated or create complications if aspirin is taken; b) directs consumers to physicians under conditions where aspirin therapy may be contraindicated, and c) warns consumers not to take aspirin if they have specific health conditions or are taking other products for which aspirin therapy may interfere. The Aspirin Foundation is aware of no basis for additional warnings.

B. Label Warnings for Aspirin Regarding Potential Nephrotoxicity are Unnecessary.

In the 1977 ANPR, the Panel concluded that in light of the available data "it is unlikely that aspirin is an initiator of serious kidney disease," even in light of prolonged use. 42 Fed. Reg. at 35407. More recent studies support this conclusion as noted by FDA in the August 2, 2002 Literature Search prepared for the Advisory Committee ("2002 Literature Search"), which stated that "normal individuals are unlikely to develop *renal failure* due to chronic use of analgesics." (emphasis added). The 2002 Literature Search does not draw

any conclusions with respect to renal diseases of less severity than renal failure. However, the 1977 Panel noted that studies suggest that "[while] aspirin may contribute to renal papillary necrosis through an additive effect . . . aspirin alone is rarely associated with renal papillary necrosis." 42 Fed. Reg. at 35407. Thus, sound science demonstrates there is minimal risk of nephrotoxicity from aspirin use.

Given the available data and prior Panel findings, a warning on aspirin products for potential nephrotoxicity is not necessary or warranted.

C. FDA Should Not Modify its Prior Determination that Label Warnings Regarding Potential Hepatoxicity from Aspirin Are Not Warranted.

The Panel in the 1977 ANPR, after reviewing extensive data, concluded that:

> [A]lthough prolonged use of high doses of aspirin may produce hepatoxicity, the effect is dose related, dependent upon the disease state for which aspirin is indicated, and is a function of any preexisting live disease. *In the opinion of the Panel, a warning that aspirin may cause liver disease is not warranted.*

42 Fed. Reg. at 35408 (emphasis added). Current warnings on aspirin include the warning noted above regarding Reye's Syndrome, which may have a hepatoxicity component.

The 2002 Literature Search does not include any hepatoxicity studies with respect to aspirin products, and currently available data do not indicate that, since the Panel's findings in 1977, long-term hepatic damage from the use of aspirin products in adults has occurred. Therefore, it is likely that the current warnings adequately inform consumers of the conditions under which aspirin may present a risk.

III. CONCLUSION

The Aspirin Foundation supports FDA in its efforts to continue its mission to ensure the health and safety American consumers. The Aspirin Foundation will continue to support FDA in its efforts to modernize and improve labeling of aspirin products based on

sound scientific principles and good data so that consumers may be better informed about the products they use. At this time, the Aspirin Foundation believes that the current warnings on aspirin product labels are sufficient to allow safe and effective use of those products, and properly to inform consumers of the potential risks of taking aspirin products. Furthermore, class labeling of OTC IAAA products is unnecessary and counterproductive to the mission of FDA to promote and ensure the safety of medications for consumers.

For these reasons, the Aspirin Foundation believes that no additional labeling is needed or warranted at this time.

Respectfully submitted,

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